PATHOLOGY AND PATHOGENESIS OF CONGENITAL TOXOPLASMOSIS*

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SYMPTOMATIC toxoplasmosis may be seen in one of several stages, accompanied by different lesions and clinical pictures, depending on when it has been transmitted *in utero* and on the time after which diagnosis is made postnatally. Asymptomatic infection may also be accompanied by some lesions which may lead to symptoms later. I shall describe the two stages of *Toxoplasma* involved, then the immunologic mechanisms which differ in the fetus and the newborn. This will be followed by a description of the four mechanisms by which lesions are produced. The paper will conclude with a description of the clinical pictures seen in children and the underlying lesions and pathology.

MICROBIAL FACTORS

Toxoplasma occurs in human tissues in two forms: 1) the tachyzoites and 2) the bradyzoites.[1] The term *tachyzoites* replaces proliferative forms and trophozoites (feeding forms), which apply to many stages. *Bradyzoites* replaces merozoites, which could be applied also to the enteroepithelial forms in the feline intestine. Tachyzoites are actively multiplying organisms which destroy infected cells, probably as a result of their competition with vital cell processes. Various numbers of intracellular tachyzoites are present in vacuoles of the host cell, and they can conveniently be designated as the "group" stage. *Group* is used in order to avoid the imprecise term pseudocyst, which has also been used as a synonym of cyst. Tachyzoites liberated from cells enter new cells and usually resume active multiplication.

The bradyzoites are slowly multiplying organisms which accumulate PAS-positive storage material and become surrounded by an

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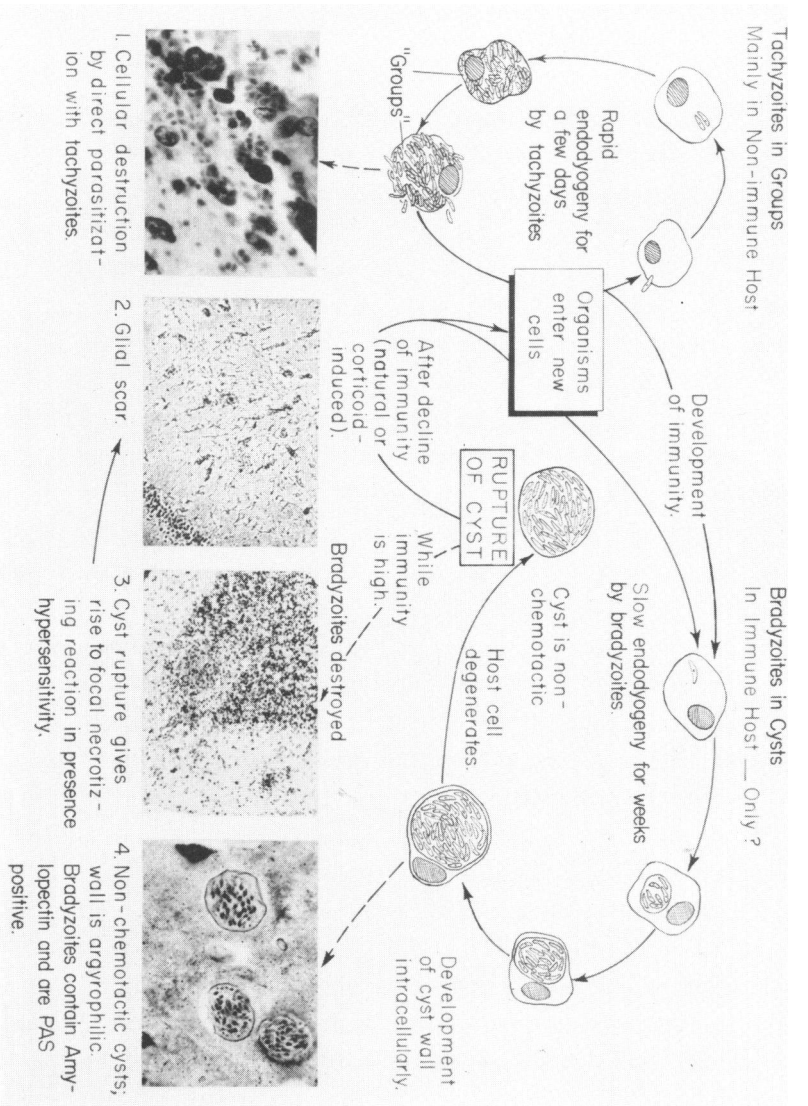

Extraintestinal or tissue cycle of *Toxoplasma* and histologic response.

argyrophilic membrane, forming the "cyst" stage. Cysts usually persist for a long time—months or years—and maintain the chronic stage of infection. The transition from the group to the cyst stage is gradual and is usually associated with a degree of immunity (see accompanying figure).

Immunity

We know nothing about the basis of natural resistance. However, it has been shown that both cells and antibody participate in immunity to toxoplasmosis.[2] From studies conducted in animals and from comparison of the transfer of cells and serum, it is inferred that cells can protect but antibody merely delays death.[3] Also, clinical and experimental studies of corticosteroids indicate that the presence of antibody is not sufficient, and that the effect of corticosteroids on lymphoid cells or macrophages impairs the expression of immunity.[4]

Immunity is achieved quickly in immunocompetent individuals such as the mothers of toxoplasmic babies. In comparison, their infants, who often suffer a protracted illness, exhibit varying degrees of immunologic deficiency. This is true although the majority of babies at birth have a level of antibody similar to that of their mothers. What was not transferred was cellular immunity.

The fact that some congenitally infected babies have no or little illness[5] suggests that they can develop a degree of immunity. It is also reasonable to suspect that some of these children are protected better *in utero* when exposed to maternal IgG than after birth, until eventually their cellular immunity becomes effective.

A second fact is that children as well as adults may show a degree of infection in the brain and eye that differs from the degree of infection in the extraneural viscera. This is clinically important and gives insight into the manner in which immunity is developed. If one follows the reduction in numbers of *Toxoplasma* and of lesions in animals recovering from infection, one finds that organisms diminish first in the blood, then in the extraneural tissues, and last in the brain and eye.

Antibody does act on extracellular organisms that are free in the bloodstream or the extracellular fluid. It is known, also, that lymphoid cells act on macrophages, rendering them specifically immune.[6] However, it is not clear how tissue cells in which *Toxoplasma* multiplies become immune. By whatever mechanisms host cells become immune, they

first make their appearance in the extraneural viscera and later in the brain and eye. By the same token, when immunosuppression has been induced by drugs, recurrent proliferation of *Toxoplasma* occurs most often in the brain and the retina. This refers to patients treated with corticosteroids or with cytostatic agents such as are employed after organ transplants or treatment of lymphoid neoplasms.[7]

Hypersensitivity

Hypersensitivity is indicated by the exaggerated inflammatory reaction in the sensitized host when compared to the inexperienced host. Immediate hypersensitivity, dependent on antibody, operates in the genesis of the periventricular zone of necrosis, to be discussed below. Delayed hypersensitivity is closely related to the presence of lymphoid cells. It gives rise to the necrosis of uninfected cells and to the exaggerated inflammatory reaction which follows rupture of cysts during chronic infection. Few if any *Toxoplasma* liberated by cyst rupture enter new cells or proliferate, which is a sign of immunity. In summary, the degree of hypersensitivity is indicated by the tissue damage following the release of antigen; the degree of immunity is shown by the limitation of microbial growth or numbers.

Lesions

Basically, we can distinguish lesions resulting from 1) the destruction of parasitized cells, mainly by tachyzoites, 2) tissue necrosis from rupture of cysts, and 3) infarction necrosis due to vascular involvement by mechanisms 1 and 2. 4) The brains of children with neonatal toxoplasmosis also show periaqueductal and periventricular vasculitis with necrosis.[8-11]

Destruction of parasitized cells by tachyzoites is the first mechanism by which lesions are produced. This is especially damaging to tissues such as the brain, the eye, and muscles, in which the cells do not regenerate. However, if the destroyed cells are replaced, as in lymphoid, epithelial, and connective tissue, or in liver and lung, lesions may not be conspicuous. Inflammatory reaction usually consists of lymphocytes, monocytes, and macrophages, with varying numbers of polymorphonuclear and sometimes plasma cells. In the brain microglial nodules are formed. In the event of extensive loss of cells or tissues, repair occurs by fibrosis and in the brain by gliosis.

Tissue necrosis following rupture of cysts usually occurs during

chronic infection in the presence of both immunity and delayed hypersensitivity. Most or all of the bradyzoites liberated by rupture are destroyed by immune processes. In spite of this, there is often necrosis of cells adjacent to the parasitized one, a manifestation of hypersensitivity. (The degree of hypersensitivity is indicated by tissue damage from antigenic release, the degree of immunity by the limitation of microbial growth or numbers.) Cysts persist in many organs, but when intact are of little significance. Likewise, rupture of cysts in liver or lymphoid tissue may be of little importance, since destroyed cells can be replaced. Even in the myocardium and brain, the rupture of a few cysts is usually not accompanied by symptoms because of the functional reserve that resides in the remaining cells. However, rupture of cysts in the retina is often symptomatic, since function is highly concentrated; the loss of a section of retina gives rise to a scotoma, and the inflammatory reaction in the vitreous obscures vision.

Infarction necrosis due to vascular involvement is not regularly present. It depends on the accidental involvement of a vessel by a parenchymal lesion which gives rise to thrombosis and infarction. Such lesions are particularly apparent in the brain since necrotic tissue in babies is prone to calcify; the focal lesion in the cerebral cortex of a baby may be so large that the calcified necrotic area becomes visible in roentgen films.

Periaqueductal and periventricular necrosis has been observed after intrauterine infection only, where there is significant parasitization of the brain.[8-11] *Toxoplasma* enters the ventricular system from parenchymal lesions and is disseminated there. It parasitizes ependymal cells and subependymal tissue, producing inflammation and causing small ulcers. If the aqueduct of Sylvius, the narrowest part of the ventricular system, becomes obstructed, the lateral and third ventricles are transformed into something like an abcess cavity, which contains accumulations of *Toxoplasma*, antigenic material, and inflammatory cells. Now another process begins. The antigenic ventricular fluid seeps through the ependymal ulcers into the subependymal tissue, coming in contact with blood vessels that carry antibody. The latter is transferred passively from the mother and is also elaborated by the fetus prior to birth. The blood vessels first show cellular infiltration of the Virchow-Robin spaces, then swelling of the cells in the vessel wall, and leakage of protein-rich fibrin (especially from the arteries). Finally the vessels

may become thrombosed. This unusual lesion is interpreted as an antigen-antibody reaction. That it is not the product of a toxic factor is shown by the presence of granulation tissue in the ventricular lumen, arising from the walls of some of the large arteries which traverse the periventricular zone of necrosis. This granulation tissue, although its vascular spaces are usually empty, is undamaged. Apparently the fluid in the ventricles is not toxic to cells.

The amount of necrotic tissue is disproportionately large compared to the number of *Toxoplasma*-containing cells, and is attributed to thrombosis. The necrotic brain tissue autolyzes and is gradually sloughed into the ventricles, from which it can be aspirated. The protein content of this ventricular fluid is high, often in the range of grams per cent. Skin tests in sensitized guinea pigs have shown that it contains antigen.[8-11]

Meanwhile, the inflammation in the unobstructed fourth ventricle, drained by the foramina of Luschka and Magendie, is minor. Ependymal ulcers are not accompanied by vascular reaction. The spinal fluid which communicates with the fourth ventricle usually contains only hundreds of milligrams per cent of protein and fewer inflammatory cells than the lateral ventricles. These lesions are illustrated and described in greater detail elsewhere.[9-11]

Pathogenesis of Clinical Pictures in Children with Congenital Toxoplasmosis

Commonly a new syndrome is recognized from fatal cases detected by pathologists. Then patients with lesser degrees of disease are traced. Finally, after the development of diagnostic techniques, asymptomatic infections are detected. In this instance the perceptive pathologists were Doctors Abner Wolf and David Cowen of the Columbia Medical Center in New York City who, 35 years ago, started to describe five children with toxoplasmic encephalitis.[12-16] These authors also observed the survival of children with congenital toxoplasmosis.[17] In most of these children, encephalitis was preponderant; but in one of their patients the lesions were generalized.[16] The technique which first permitted diagnosis of toxoplasmosis as an infection, irrespective of a clinical picture, was the dye test developed by Sabin and Feldman[18] 25 years ago. This test was based on a new phenomenon, which specifically and sensitively detected the presence of antibody and provided a tool with

which the broad range of manifestations of toxoplasmosis, including asymptomatic infection, could be recognized.

Transmission. Toxoplasmosis is usually acquired by mouth, either from cysts in meat or via oocysts from cats and soil. The fetus is infected parenterally via the umbilical vein, and organisms from the placenta[19, 20] reach the liver first. From the various portals of entry there is dissemination by way of the bloodstream and the lymphatics. The organisms lodge in many organs, producing small lesions.[16, 21-23] Manifestations such as pneumonia and myocarditis are readily explained by the destruction of tissue cells by *Toxoplasma.* However, to produce jaundice, encephalitis, and retinochoroiditis the pathogenesis is complex.

Jaundice may be prominent; it is attributed to hepatitis and to hemolytic phenomena. This is part of acute toxoplasmosis. The hepatitis may be of the giant-cell variety seen in newborn children and believed to be due to a variety of causes.[24] Hemolysis has been shown to play an additional role. In several instances the diagnosis of erythroblastosis was made in addition to that of visceral toxoplasmosis.[22-25] Toxoplasmosis may resemble cytomegalovirus disease, from which it should be differentiated.[26, 27]

Encephalitis is at first disseminated. Lesions consist of numerous glial nodules similar to those encountered in certain viral encephalitides. As mentioned already, immunity is acquired more slowly in the central nervous system than in the extraneural viscera. One often sees progressive lesions in the brain and eye, together with subsiding pneumonia and hepatitis.[11] Encephalitis may progress slowly, especially in an infant. Such a child may be premature, in any case less immunocompetent than his mother. This is why some babies who have asymptomatic encephalitis at birth may develop intellectual deficits later,[28] or even cerebral calcifications.[29] In the presence of moderately severe encephalitis, a microglial nodule may involve the ependyma and seed *Toxoplasma* into the ventricular system. This intraventricular dissemination leads to parasitization of many ependymal cells, ulceration of the ventricular lining, and obstruction of the aqueduct of Sylvius. Periventricular lesions may form; their pathogenesis has been described above and is illustrated elsewhere.[9-11, 30] These lesions are very destructive and almost always produce symptoms. The tetrad of signs—convulsions, cerebral calcification, internal hydrocephalus, and retinochoroiditis—has been ascribed to this lesion by Sabin.[31] If hydrocephalus is present, the ven-

tricular fluid often contains grams rather than milligrams of protein per 100 ml., whereas the spinal fluid contains only hundreds of milligrams per 100 ml. In such cases, the diagnosis of toxoplasmosis is probable if meningitis caused by *E. coli* can be excluded by smear or culture. Fluid from the distended ventricles is most useful for diagnostic purposes, since it contains *Toxoplasma* which can be recovered in animals and antigen which can be demonstrated—as well as a high-protein content which is almost diagnostic.

In view of the aqueductal obstruction, such children develop hydrocephalus and extensive cerebral destruction. Necrotic brain tissue often calcifies and becomes visible in x-ray films. Involvement of the hypothalmus around the third ventricle can lead to instability of body temperature.

Retinochoroiditis usually accompanies severe neonatal toxoplasmosis. It may also appear in older children and adults who had no symptoms at birth, although not all such lesions should be ascribed to congenital infection. Since function is so highly concentrated in the retina, even a small lesion can be clinically significant, especially when it is in or near the macula.[32] In children who died with congenital toxoplasmosis, active and healed lesions have been observed. Histologically, tachyzoites and cysts were seen.[11, 22, 33] Most of the lesions in these infants appear to have resulted from tachyzoites; the lesions are larger than those in older children and adults. The persistence of cysts in the retina, even in children who showed few symptoms in the first year of life, predisposes to lesions later on; occasionally these progress to blindness and glaucoma.[29] In contrast, most of the lesions observed in children and adults are of the cyst-rupture type. They are sudden in onset and usually heal, apparently because of immunity. However, the use of corticosteroids can lead to immunosuppression, the proliferation of tachyzoites, and progressive lesions unless prevented by sulfadiazine and pyrimethamine or other suppressive treatment.

Summary

The pathogenesis of congenital toxoplasmosis is basically similar to that of the adult form. However, because of prematurity and the general immunologic immaturity of infants, the lesions may be more severe. This is apparent when infected children are compared with their mothers who are infected with the same strain of *Toxoplasma;*

in spite of the transfer of antibody from the mother to the infant *in utero*, the infection in the neonate is more severe. This is probably due to deficiency in the cellular immunity acquired, and related to biologic immaturity. As a consequence, the infection remains active longer in the neonate. This allows greater parasitization of the brain and eye, which acquire immunity more slowly than the extraneural viscera. Actually, toxoplasmosis of the central nervous system and eye may progress silently. Frank encephalitis with hydrocephalus and periventricular necrosis may also develop. The latter lesion results from an antigen-antibody reaction *in vivo*.

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